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ORIGINAL RESEARCH

Derivatives of benzo[*b*]furan. Part II. Structural studies of derivatives of 2- and 3-benzo[*b*]furancarboxylic acids

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Abstract The selected derivatives of the 2- and 3-benzo[*b*]furancarboxylic acids were synthesized and their structures were studied using the X-ray crystallography and the computational methods. The monocarboxylic acids (**1**–**3**) crystallize as dimers stabilized by the O–H···O intermolecular hydrogen bonds. Moreover, intramolecular hydrogen bonds are formed between the OH and $C(=O)CH_3$ groups, substituted to the aromatic ring (**2**–**4**). In the crystal structures of **1**–**4**, weak C–H···O, C–H···π, and C–H···Br interactions stabilize the three-dimensional packing of molecules. The crystalline sodium complex of **1** has the stoichiometry [$\mathbf{Na^+ \cdot 1A^- \cdot 1B}$]·**1C**, thus, the asymmetric unit contains three different moieties of **1**. In this complex, the Na^+ cation is hexacoordinated having a strongly distorted tetragonal bipyramidal polyhedron. For each molecule **1**–**4**, several conformers were obtained in the gas phase. It was achieved by the rotations of substituents [COOR and/or $C(=O)CH_3$, where R = H, CH_3] with respect to the rigid benzo[*b*]furan system. As indicated by the quantum-chemical calculations, the solid-state conformers for **3** and **4** (3-benzo[*b*]furancarboxylic acid derivatives) are the most stable ones. In contrast, the solid-state conformers of the 2-benzo[*b*]furancarboxylic acid derivatives (**1**, **2**) have the energies higher than the lowest energy conformer by 1.23 and 0.69 kcal/mol, respectively. It seems that intermolecular contacts in the crystal influence on the orientation of substituents, and the conformers observed in the sodium complex of **1** provide evidence of such flexibility.

Keywords Benzo[*b*]furan derivatives · Conformational analysis · Theoretical calculations · Crystal structure

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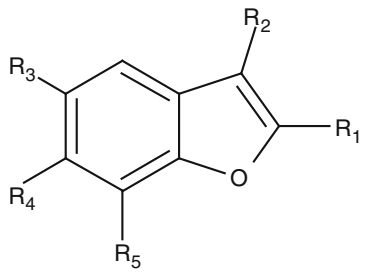
Introduction

The benzofuran derivatives, isolated from natural sources as well as synthetic, show cytostatic and/or antitumor activity (e.g., [1–9]). Therein, neolignans isolated from the *Persea* species are cytotoxic in vitro to the human cancer cell lines: mouth epidermoid carcinoma, lung adenocarcinoma, and colon adenocarcinoma [7]. Recently, it was proved that derivatives of the 2- and 3-benzo[*b*]furancarboxylic acids showed also selective cytotoxicity against

the human cancer cell lines [8, 9]. Moreover, the compounds containing the benzo[*b*]furan system show antiprotozoal and/or antifungal activity [10–13], e.g., amiodarone, a drug used as an antiarrhythmic agent, possess significant antifungal potential [14–19]. The derivatives of 2- and 3-benzo[*b*]furan-carboxylic acids, especially those containing halogen atom (Br or Cl) in their structure, are active against the *Candida* strains *C. albicans* and *C. parapsilosis* [20, 21], *Mycobacterium tuberculosis* [22] and are selective Pim kinase inhibitors [23].

Due to the wide spectrum of biological activity of such aromatic monocarboxylic acids, it is important to describe their molecular structure and patterns of intermolecular contacts. However, the papers on the molecular structure of relatively simple benzo[*b*]furan derivatives are very scarce and there is no report on the structure of any benzo[*b*]furan-monocarboxylic acid (see Supplementary Material). In this study, we present the conformational analysis of 7-acetyl-6-methoxy-3-methylbenzo[*b*]furan-2-carboxylic acid (**1**), 7-acetyl-5-bromo-6-hydroxy-3-methylbenzo[*b*]furan-2-carboxylic acid (**2**), 6-acetyl-5-hydroxy-2-methylbenzo[*b*]furan-3-carboxylic acid (**3**), and methyl ester of 6-acetyl-5-hydroxy-2-methylbenzo[*b*]furan-3-carboxylic acid (**4**) (Fig. 1). Moreover, the sodium complex (**5**) of the acid **1** has been synthesized. This compound is the first metal complex of benzo[*b*]furan-monocarboxylic acid for which the stereochemistry is determined. So far, the ammonium salts and transition metal complexes of benzo[*b*]furan-2,3-dicarboxylic acid have been analyzed by Goldberg et al. [24–27].

The main goal of this study is to describe the stereochemistry of the *O*-donor groups of investigated compounds. To achieve this goal, an X-ray crystallography was used and the theoretical calculations were performed to find all stable conformers of the derivatives of 2- and 3-benzo[*b*]furancarboxylic acids.



	R_1	R_2	R_3	R_4	R_5
1	COOH	CH_3	H	OCH_3	$C(=O)CH_3$
2	COOH	CH_3	Br	OH	$C(=O)CH_3$
3	CH_3	COOH	OH	$C(=O)CH_3$	H
4	CH_3	$COOCH_3$	OH	$C(=O)CH_3$	H

Fig. 1 Chemical structure of the investigated compounds **1**–**4**

Experimental

Synthesis of ligands (**1**–**4**)

The chemicals were obtained from Sigma-Aldrich. The compounds **1**–**4** were synthesized according to the previously published papers [28–30]. Single crystals suitable for the X-ray diffraction were prepared by a slow evaporation of the solvent from the ethanolic solutions at room temperature; however, the crystals of **2** were of poor quality.

The IR spectra were performed between 4,000 and 400 cm^{-1} on a Perkin Elmer 1725× FT-IR spectrometer using the KBr pellets. The characteristic bands (cm^{-1}) observed for compounds **1**–**4** are

1: 3424 (ν O–H), 1694 (ν C=O), 1677 (ν C=O), 1449 (δ COH), 1383 (δ^s CH_3), 1363 (δ^s CH_3), 1281 (ν C–O)
2: 2924 (ν O–H), 1685 (ν C=O), 1634 (ν C=O), 1448 (δ COH), 1371 (δ^s CH_3), 1213 (ν C–O), 1153 (ν C–O)
3: 3084 (ν O–H), 1685 (ν C=O), 1623 (ν C=O), 1420 (δ COH), 1368 (δ^s CH_3), 1197 (ν C–O), 1186 (ν C–O)
4: 3402 (ν O–H), 1717 (ν C=O), 1641 (ν C=O), 1372 (δ^s CH_3), 1199 (ν O–C(=O)), 1152 (ν C–OH), 1091 (ν C(=O)–O)

Synthesis of complex (**5**)

The chemicals were obtained from Sigma-Aldrich. The sodium hydride was used as a deprotonation agent and as a source of Na cations [31, 32]. The ligand **1** (0.4 mmol) and sodium hydride (0.4 mmol) in 10 mL of ethanol solution were refluxed for 3 h in 30 °C. After several days, colorless crystals of sodium complex (**5**) were obtained.

X-ray crystallography

The diffraction data for the crystals of **1**–**5** were collected on Oxford Diffraction KM4 or Xcalibur diffractometers. The structures were solved by direct methods using the SHELXS-97 program and refined by the full-matrix least-squares method on F^2 using the SHELXL-97 program [33]. The non-hydrogen atoms were refined with anisotropic displacement parameters. The C-bonded H-atoms were positioned geometrically and allowed to ride on the attached atom. The primary positions of the O-bonded H-atoms were taken from the difference electron-density maps and they were riding during the refinement with the fixed O–H distance. The isotropic displacement parameters of the H-atoms were $U_{iso}(H) = 1.3\ U_{eq}(C)$ for the methyl groups and $U_{iso}(H) = 1.2\ U_{eq}(C/O)$ for the rest of atoms. The structural data for the poor-quality crystal of **2** were also included to the discussion. The crystallographic data, details of the data collection and refinement are given in Table 1.

Computational details

The calculations were performed using the Gaussian03 program package [34] and the procedure tested previously for benzo[*b*]furans [35]. The geometry of molecules **1**–**4** in the gas phase was optimized with the B3LYP [36, 37] exchange–correlation potential, using a standard 6-31G(d) basis set [38]. The atomic coordinates found in the solid state were used as the initial guess. The PES scan study has been performed for the molecules **1**–**4**. The scans started from the zero value of the torsion angle up to ±180°, with a step size of 10°. The geometry of conformers corresponding to the minima on the PES was optimized with the B3LYP method using 6-31++G(d,p) basis set. The vibrational frequency calculations were performed for the found conformers and all frequencies were real.

Results and discussion

Structural analysis of ligands (**1**–**4**)

Molecular structure in solid

The rigid aromatic benzo[*b*]furan system is substituted by several groups containing O-atoms, viz. OH, OCH_3, $C(=O)CH_3$, and $COOH/COOCH_3$. In the crystal structures of **2** and **3**, there are two molecules in the asymmetric part,

Table 1 Crystal data and experimental parameters

Compounds	**1**	**2**	**3**	**4**	**5**
Empirical formula	$C_{13}H_{12}O_5$	$C_{12}H_9Br_1O_5$	$C_{12}H_{10}O_5$	$C_{13}H_{12}O_5$	$Na_1C_{39}H_{35}O_{15}$
Formula weight	248.23	313.10	234.20	248.23	766.66
Crystal system	Monoclinic	Orthorhombic	Orthorhombic	Monoclinic	Monoclinic
Space group	*C2/c*	$Pca2_1$	*Pbca*	$P2_1/c$	*Cc*
a (Å)	13.007(3)	10.514(4)	13.274(3)	10.242(2)	14.391(3)
b (Å)	10.525(2)	22.607(9)	8.711(2)	16.826(3)	17.624(4)
c (Å)	16.965(3)	9.663(4)	36.408(7)	7.041(1)	15.766(3)
α (°)	90	90	90	90	90
β (°)	97.46(3)	90	90	105.98(3)	114.58(3)
γ (°)	90	90	90	90	90
V (Å^3)	2302.8(8)	2296.8(16)	4209.9(16)	1166.5(4)	3636.3(13)
Z/*Z*′	8/1	8/2	16/2	4/1	4/1
d (g/cm^3)	1.432	1.811	1.478	1.413	1.400
Absorption coeff. (mm^{-1})	0.937	3.590	0.990	0.925	1.015
F(000)	1,040	1,248	1,952	520	1,600
Crystal size (mm)	0.40 × 0.38 × 0.38	0.36 × 0.12 × 0.10	0.38 × 0.15 × 0.14	0.34 × 0.22 × 0.21	0.39 × 0.39 × 0.37
Temperature (K)	293(2)	100(2)	293(2)	293(2)	293(2)
λ (Å)	1.54178	0.71073	1.54178	1.54178	1.54178
θ range for data collection (°)	5.26–75.15	4.28–32.61	2.43–75.15	5.20–75.13	4.21–77.18
Index ranges	$-16 \le h \le 16$	$-15 \le h \le 15$	$-16 \le h \le 0$	$0 \le h \le 12$	$-18 \le h \le 16$
	$-13 \le k \le 13$	$-34 \le k \le 26$	$-10 \le k \le 10$	$-21 \le k \le 0$	$-22 \le k \le 22$
	$0 \le 1 \le 21$	$-14 \le l \le 14$	$-45 \le l \le 45$	$-8 \le l \le 8$	$0 \le l \le 18$
Reflections collected	4,728	22,593	16,368	2,538	7,367
Independent reflections	2,385	7,962	4,327	2,407	3,811
Observed reflections [$I > 2\sigma(I)$]	2,032	2,978	1,397	1,217	1,825
Parameters	142	330	294	151	508
Goodness of fit on F^2	1.040	0.794	0.943	1.035	0.950
R1 [$I > 2\sigma(I)$]	0.0384	0.0662	0.0698	0.0601	0.0545
wR_2 [$I > 2\sigma(I)$]	0.1071	0.1582	0.2129	0.1461	0.1393
Δ*ρ* max./min. (e Å^{-3})	0.25/−0.18	1.38/−1.07	0.33/−0.33	0.26/−0.23	0.73/−0.21
CCDC No[a]	849 116	849 117	849 118	849 119	849 120

[a] Copies of the data can be obtained free of charge on request via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk

labeled as **A** and **B**, thus, six molecular structures are compared. The bond lengths and angles of the molecules are within the expected ranges and are equal within the experimental error. The atom numbering and the conformations of **1**–**4** adopted in the crystal are shown in Fig. 2.

The molecules of the studied compounds contain the acetyl group connected to the atom C7 in the molecules **1**, **2** or C6 in **3**, **4**. The *ortho*-position of the acetyl and methoxy groups in acid **1** causes out-of-the-plane deviation of the acetyl fragment; the interplanar angle of the aromatic ring and this group is 45.7(9)° (Table 2). The methoxy group, present in **1**, is coplanar with the aromatic ring (Table 2). The coplanarity of the methoxy group to the benzo[*b*]furan system and the rotation of the acetyl substituent is also observed in the molecular structures of two khellinone dimers [39, 40].

The *ortho*-position of the acetyl and hydroxyl groups present in two other acids (**2**, **3**) and ester (**4**) promotes the formation of the $O–H_{hydroxyl}\cdots O_{acetyl}$ intramolecular hydrogen bond in the $S_1^1(6)$ motif [41] (Fig. 3; Table 3), which causes the coplanarity of the acetyl and benzo[*b*]-furan moieties (Table 2). These are consistent with the stereochemistry of the analogous compounds [42, 43].

The coplanarity of the carboxylic/ester group with the aromatic ring is observed for all investigated compounds (**1**–**4**) (Table 2). The dihedral angle $C_{Ar}–C(=O)–O/Ar$, where C_{Ar} is an aromatic C atom and Ar is an average plane passing through the aromatic system, equals 1.8(4)°,

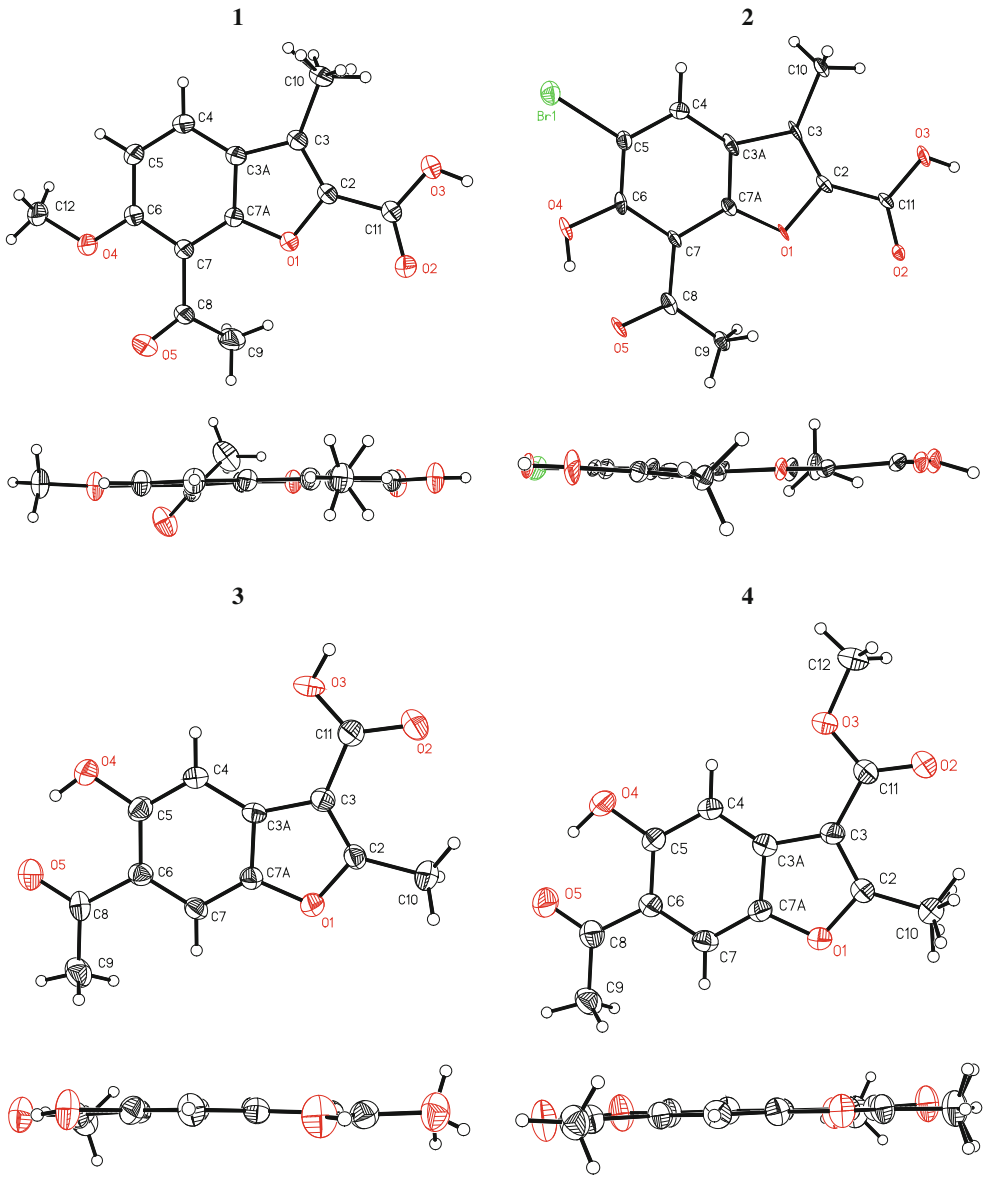


Fig. 2 Molecular structures of **1**–**4** with thermal ellipsoid plot and atom-numbering scheme. View perpendicular and parallel to benzo[*b*]furan system

4.1(5)°, 1.3(4)°, 2.4(4)°, 2.4(3)°, 4.8(1)°, for the molecules **1**, **2A**, **2B**, **3A**, **3B**, and **4**, respectively.

The carbonyl C=O bond of the C_{Ar}–C(=O)–OH fragment is in the *trans* (**1**, **2**) or *cis* (**3**, **4**) orientations with respect to the neighboring C–CH_3 bond (Fig. 2). This orientation is consistent with other structural data [44, 45].

Crystal structure

The intramolecular O–H···O hydrogen bond, formed in the molecules **2**–**4**, is accompanied by the intermolecular O–H···O bonds in the crystal structure of the carboxylic acids (**1**–**3**) (Fig. 3; Table 3). The carboxyl group, acting as a donor and acceptor in this contacts, creates dimers in the $R_2^2(8)$ motif [38, 39], typical for the carboxylic acids. In the crystal **1**, the centrosymmetric dimers are formed (**1**·**1**), whereas in the crystals **2** and **3** the structural units are pairs of symmetry independent molecules (**2A**·**2B** and **3A**·**3B**). The molecular dimers (**1**–**3**) or monomers (**4**) are linked by the C–H···O, C–H···π, and C–H···Br contacts (Table 4) and the molecular stacks in the crystals of **1**–**4** are observed (Fig. 4).

Conformational analysis in gas phase

Since the benzo[*b*]furan system is rigid, the potential energy surface (PES) for the internal rotation about the $\mathbf{C}_{Ar}$–**C**(=O) single bonds in the molecules **1**–**4** has been explored using quantum-chemical methods.

The search for stable conformers was focused on the rotation of COOH/$COOCH_3$ group for all molecules and the C(=O)CH_3 substituent for **1**. The changes of the orientation of the acetyl group for other molecules were not considered, because in the molecules **2**–**4** this substituent is involved in a strong O–H···O intramolecular hydrogen bond and it is unlikely to obtain a different orientation of the acetyl group than that observed in the crystals [34].

To find stable conformers of the acid **1**, the PES for the O5–C8–C7–C7A torsion angle has been scanned within the isolated molecule (Fig. 5). The restricted rotation about the **C**7–**C**8(=O)CH_3 single bond yields two stable conformations: **1.1** and **1.2** (Fig. 6). The molecule **1.1** has the carbonyl group of the **C**8(=**O**)CH_3 substituent in the *trans* orientation with respect to the **C**7A–**O**1 bond. The second conformer **1.2**, energetically less favorable ($\Delta E = 0.17$ kcal/mol), is

Table 2 Selected torsion angles (°) for molecules **1**–**4** observed in solid

	C(=O)CH_3		COOH/$COOCH_3$		OCH_3	
1	O5–C8–C7–C6	−43.8(2)	O2–C11–C2–C3	177.6(8)	C12–O4–C6–C5	1.8(2)
2A		−5.1(1)		179.6(9)		
2B		−4.1(1)		−178.3(9)		
3A	O5–C8–C6–C5	3.4(1)	O2–C11–C3–C2	3.7(1)		
3B		−4.4(1)		−0.7(8)		
4		0.8(4)		−4.6(4)		

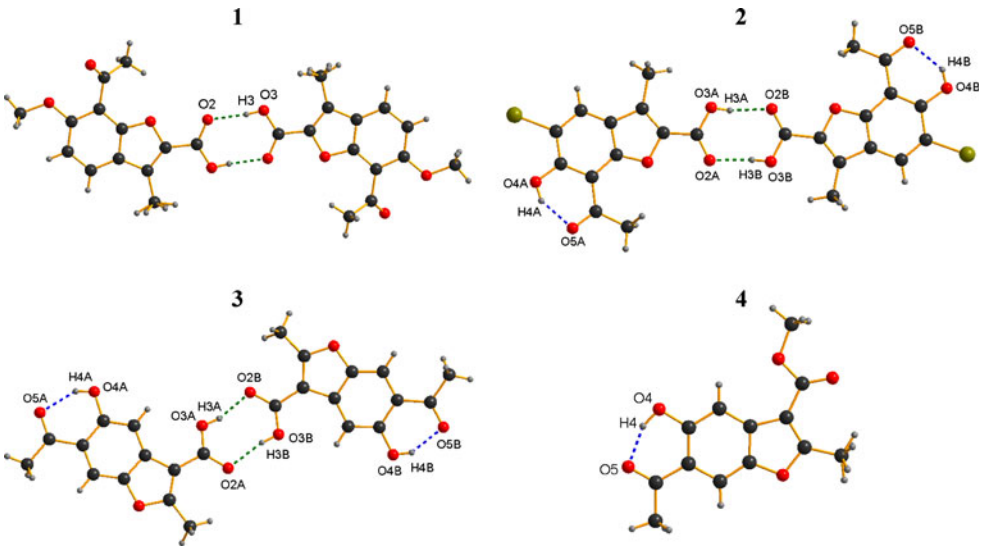


Fig. 3 Intra- and intermolecular O–H···O hydrogen bonds observed in crystals **1**–**4**

Table 3 Geometric parameters of O–H···O hydrogen bonds in crystals **1–4**

	D–H···A	d(D–H) (Å)	d(H···A) (Å)	d(D···A) (Å)	<D–H···A (°)
1	O3–H3···O2^{i}	0.82	1.82	2.635(1)	172
2	O3A–H3A···O2B	0.84	1.83	2.593(8)	150
	O3B–H3B···O2A	0.84	1.81	2.620(8)	160
	O4A–H4A···O5A	*0.84*	*1.78*	*2.529(9)*	*147*
	O4B–H4B···O5B	*0.84*	*1.86*	*2.542(8)*	*137*
3	O3A–H3A···O2B	0.82	1.79	2.573(6)	158
	O3B–H3B···O2A	0.82	1.87	2.678(6)	167
	O4A–H4A···O5A	*0.82*	*1.84*	*2.563(8)*	*146*
	O4B–H4B···O5B	*0.82*	*1.79*	*2.530(8)*	*148*
4	*O4–H4···O5*	*0.92*	*1.68*	*2.549(3)*	*155*

Italicization indicates intramolecular hydrogen bond

Symmetry codes: (*i*) $-x + 1/2$, $-y + 1/2$, $-z + 1$

Table 4 Geometric parameters of C–H···O, C–H···Br, and C–H···π (C_g) contacts in crystals **1–4**

	D–H···A*	d(D–H) (Å)	d(H···A) (Å)	d(D···A) (Å)	<D–H···A (°)	*Symmetry code for A
1	C9–H9A···O2	0.96	2.48	3.413(2)	163	$1 - x, y, 3/2 - z$
	C12–H12B···O4	0.96	2.55	3.409(2)	149	$2 - x, y, 3/2-z$
	C12–H12B···O5	0.96	2.65	3.455(2)	142	$2 - x, y, 3/2 - z$
	C9–H9C···O5	0.96	2.52	3.422(3)	157	$3/2 - x, 1/2 + y, 3/2 - z$
	C4–H4···O5	0.96	2.67	3.576(3)	166	$x, -y, -1/2 + z$
	C10–H10D···O3	0.96	2.40	3.085(1)	128	
	C9–H9B···O1	0.96	2.31	3.008(3)	129	
2	C10A–H10C···O5A	0.98	2.60	3.388(11)	138	$-1 + x, y, z$
	C9B–H9D···O1A	0.98	2.69	3.397(9)	129	$1/2 - x, y, -1/2 + z$
	C10B–H10F···O5B	0.98	2.59	3.408(10)	141	$1+x, y, z$
	C10A–H10C···O3A	0.98	2.46	3.049(13)	118	
	C9A–H9B···O1A	0.98	2.44	2.886(10)	107	
	C10B–H10F···O3B	0.98	2.35	3.034(11)	126	
	C9B–H9D···O1B	0.98	2.40	2.811(9)	105	
	C10A–H10A···Br1A	0.98	3.01	3.871(11)	147	$1 - x, 1 - y, -1/2 + z$
	C10A–H10B···Br1A	0.98	2.82	3.609(12)	138	$-1/2 + x, 1 - y, z$
	C9A–H9B···C_gA	0.98	2.96	3.854(13)	152	$3/2 - x, y, -1/2 + z$
3	C7A–H7A···O4A	0.93	2.53	3.177(9)	127	$1/2 + x, 3/2 - y, -z$
	C10A–H10C···O5B	0.96	2.55	3.455(8)	158	$1/2 + x, 1 + y, 1/2 - z$
	C7B–H7B···O4B	0.93	2.42	3.283(7)	155	$-1/2 + x, y, 1/2 - z$
	C10A–H10B···O2A	0.96	2.46	3.077(10)	122	
	C10B–H10E···O2B	0.96	2.51	2.965(8)	109	
	C9A–H9B···C_gA	0.96	3.00	3.930(11)	165	$2/3 - x, 1/2 + y, z$
	C10B–H10F···C_gB	0.96	3.52	4.041(8)	117	$1/2 - x, 1/2 + y, z$
4	C10–H10D···O2	0.96	2.38	3.053(4)	127	
	C10–H10F···O4	0.96	2.70	3.492(4)	140	$1 + x, y, z$
	C12–H12A···O5	0.96	2.63	3.516(4)	154	$-x, -1/2 + y, 1/2 - z$
	C7–H7···O2	0.93	2.48	3.409(4)	176	$1 - x, 1/2 + y, 1/2 - z$
	C9–H9B···C_g	0.96	2.98	3.887(4)	159	$x, 1/2 - y, -1/2 + z$
	C9–H9C···C_g	0.96	2.71	3.618(4)	157	$x, 1/2 - y, ½ + z$

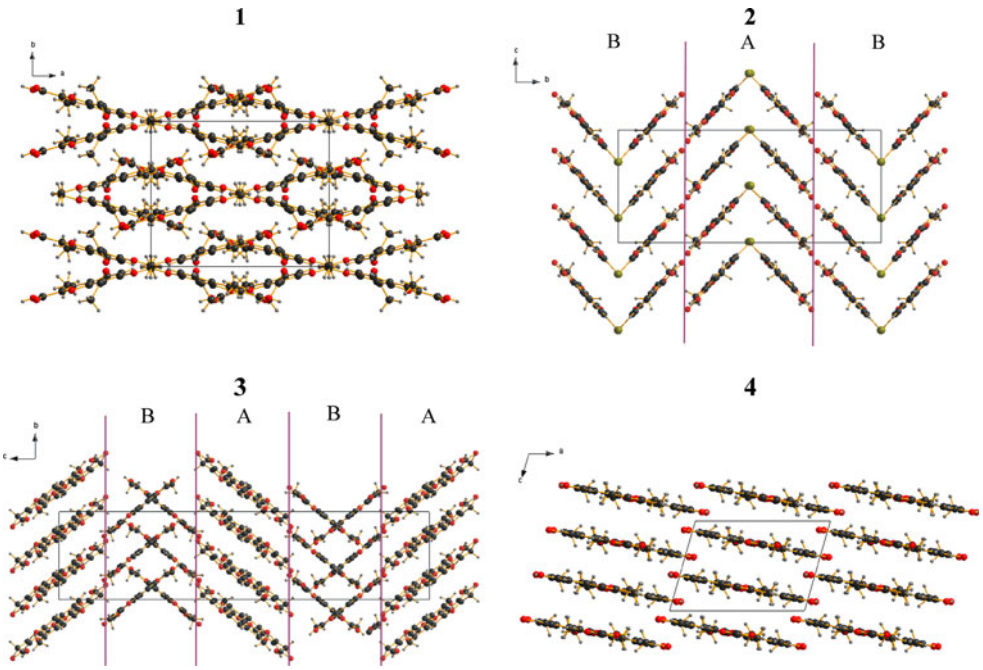


Fig. 4 Comparison of crystal packing of **1**–**4**. For **2** and **3**, columns of symmetry-independent molecules are marked

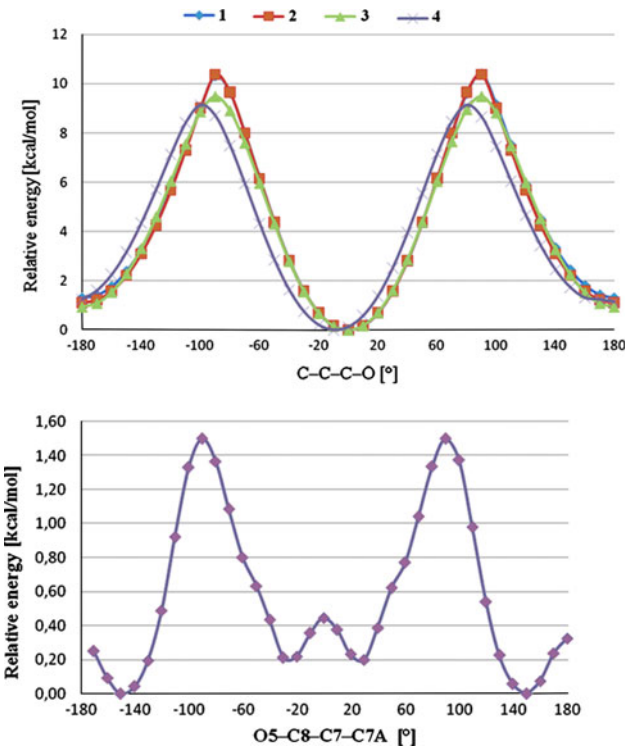


Fig. 5 PES calculated for rotation of carboxyl/ester groups of **1**–**4** (*top*) and acetyl group of **1** (*bottom*)

characterized by the *cis* conformation of those fragments. The molecular structure of the most stable conformation in the gas phase (**1.1**) is in agreement with the stereochemistry of molecules adopted in the solid (Tables 2, 5).

For all calculated conformers, the carboxyl or ester group is coplanar with the aromatic ring (Table 5). There are two possible relative orientations of the C=O bond (of the $COOH/COOCH_3$ substituent) and the C2/C3–CH_3 single bond: *trans* (**1.1**, **1.2**, **2.1**, **3.2**, **4.2**) and *cis* (**1.3**, **1.4**, **2.2**, **3.1**, **4.1**) (Fig. 6). The calculated electron energies for all conformers indicate that the *cis* orientation of C11=O2 and C2/C3–CH_3 bonds is energetically more favorable.

Additional conformers, less populated, were found by changing the orientation of hydroxyl group for the acid molecules **1**–**3**. By the rotation around the **C**11–**O**3(H) single bond, two conformations of COOH group can be distinguished for **2**, **3** (Fig. 6), and for **1** (Fig. 7). The –OH group adopts either a synplanar or antiplanar conformation of the O=C–O–H moiety, where the synplanar structure is the most stable form. According to the literature, in the crystalline state, the antiplanar O=C–O–H form occurs when the O–H bond participates in an intramolecular O–H···O bond. This is observed for the 1,2-substituted dicarboxylic acids [46], e.g., 1-benzofuran-2,3-dicarboxylic acid and its ammonium salts [23–25]. Taking into account, the combinations of orientation of the $COOH/COOCH_3$ group, four conformers of the acids **2** and **3**, and two conformers of the ester **4** are predicted (Fig. 6).

For the acid **1**, three orientations of the methoxy group are possible (Fig. 7). If all rotations for the molecule **1** are considered, viz. around the $\mathbf{C}_{Ar}$–$\mathbf{C}(=O)CH_3$, $\mathbf{C}_{Ar}$–COOH and $\mathbf{C}_{Ar}$–$\mathbf{O}CH_3$ single bonds, 16 conformers will be found (Fig. 7).

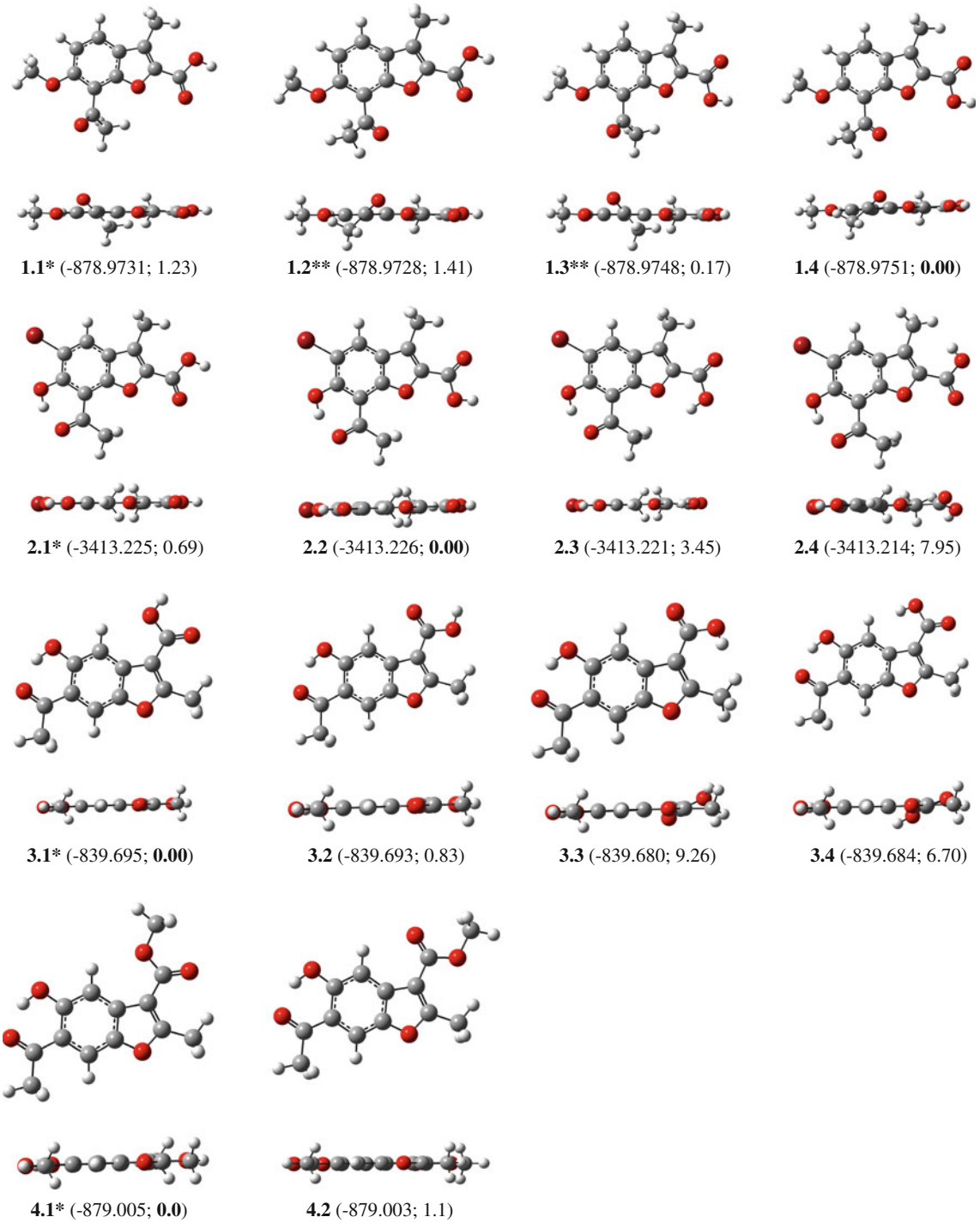


Fig. 6 Selected conformers of acid **1** and all conformers of molecules **2**, **3**, and **4.** Values in *brackets* indicate calculated energy in hartree and relative energy in kcal/mol. *Solid-state conformer in respective crystals **1**–**4.** **Solid-state conformer in crystal **5**

Structural analysis of sodium complex (**5**)

Molecular structure

The asymmetric part consists of the Na^+ cation and three organic units: **1A**—the anion of compound **1**, coordinating to Na^+, **1B**—the molecule of acid **1** coordinating to Na^+ cation, and **1C**—the molecule of compound **1** cocrystallizing outside of the Na^+ coordination sphere: [$\mathbf{Na^+}$·**1A**$^-$·**1B**]·**1C** (Fig. 8). The units **1A** and **1B** are tridentate ligands chelating through the O-atoms, i.e., O1 from the furan ring, O5 of the acetyl group and O2 of the

carboxylate (**1A**) or the carboxyl group (**1B**), respectively. Thus, the Na^+ exhibits sixfold coordination and a strongly deformed tetragonal bipyramid is formed (Fig. 9; Table 6). The Na–O bond distances are in the range 2.358(7)–2.461(6) Å (Table 6).

Table 5 Selected torsion angles (°) of conformers in the gas phase for molecules **1–4**

	$C(=O)CH_3$		COOH/ $COOCH_3$		OCH_3	
1.1	O5–C8–C7–C6	−48.2	O2–C11–C2–C3	−177.5	C12–O4–C6–C5	−5.7
1.2		46.6		−176.6		0.5
1.3		−50.1		1.0		−5.9
1.4		−138.8		0.8		0.7
2.1		0.0		180.0		
2.2		0.0		0.0		
2.3		0.0		180.0		
2.4		0.4		159.3		
3.1	O5–C8–C6–C5	0.0	O2–C11–C3–C2	0.0		
3.2		0.0		180.0		
3.3		−0.1		−28.6		
3.4		0.0		−22.8		
4.1		0.0		0.0		
4.2		0.0		180.0		

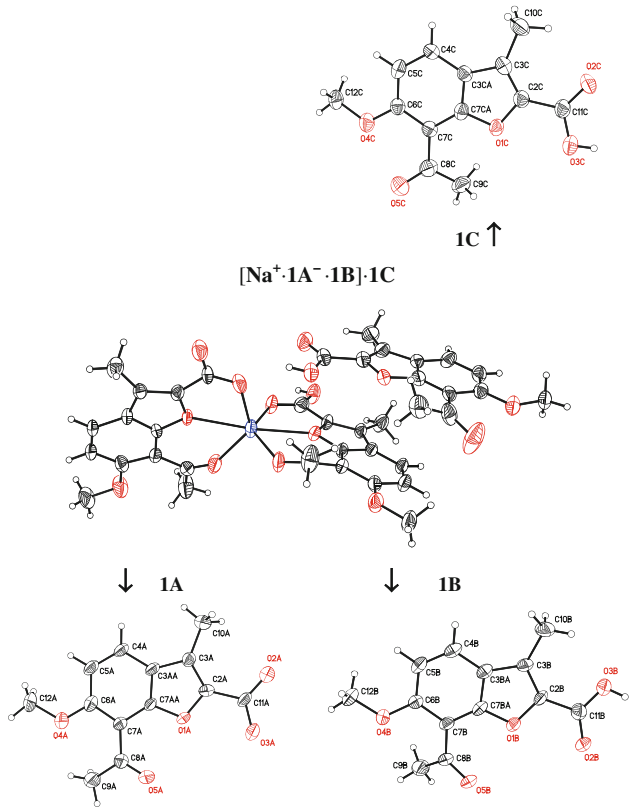
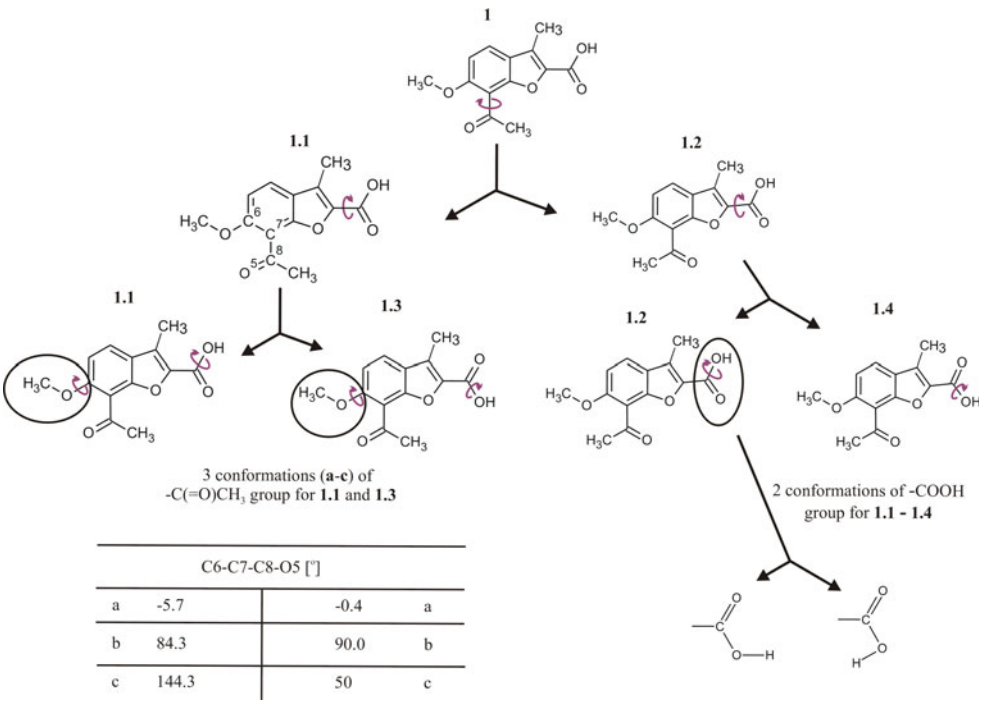


Fig. 8 Molecular structure of **5** with thermal ellipsoid plot and atom-numbering scheme of organic components

Fig. 7 All conformers of acid **1**



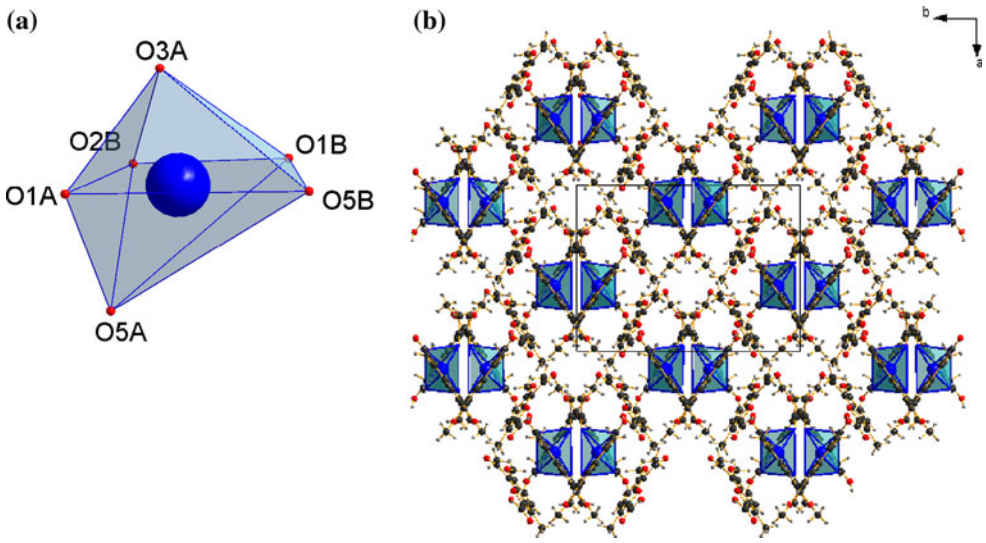


Fig. 9 Coordination polyhedron of Na in complex **5** (**a**) and packing of complex units in crystal (**b**)

Stereochemistry of ligands

There are no significant differences between the respective bond distances and valence angles for the three organic units **1A**, **1B**, and **1C**. However, the values of torsion angles describing the orientations of the *O*-donor groups vary (Table 7). For the anion **1A** and acid **1B**, which chelate to Na^+, the C8=O5 acetyl and furan O1–C7A bonds are the *cis* oriented, thus the O5 carbonyl atom is included into the coordination sphere of Na^+ (Fig. 9a). For the non-coordinating acid molecule **1C**, the *trans* orientation of the respective bonds is observed. The $C(=O)CH_3$ substituent of all conformers **1A**, **1B**, and **1C** is tilted out-of-the-average mean plane determined by the aromatic atoms (Table 7). Furthermore, the acid molecules, **1B** and **1C**, have different conformations of the carboxyl group; the C11=O2 and C3–C10H_3 bonds have the *trans* orientation for the chelating molecule **1B**, and *cis* for **1C** (Fig. 8). The methoxy group is coplanar with the benzo[*b*]furan system for all conformers (Table 7).

Table 6 Selected bond distances and valence angles for Na^+ coordination sphere in **5**

Na–O (Å)	
Na1–O1A	2.461(6)
Na1–O5A	2.377(7)
Na1–O3A	2.358(7)
Na1–O1B	2.444(6)
Na1–O5B	2.417(6)
Na1–O2B	2.379(7)
O–Na–O (°)	
O3A–Na1–O2B	110.7(2)
O3A–Na1–O1B	107.4(2)
O3A–Na1–O1A	66.2(2)
O5A–Na1–O2B	87.9(3)
O5A–Na1–O5B	112.8(2)
O5A–Na1–O1B	119.5(2)
O5A–Na1–O1A	67.0(2)
O5B–Na1–O1B	68.4(2)
O3A–Na1–O5A	133.1(2)
O1B–Na1–O1A	173.1(2)
O2B–Na1–O5B	134.8(2)
O3A–Na1–O5B	84.5(2)
O2B–Na1–O1A	112.7(2)
O2B–Na1–O1B	66.6(2)
O5B–Na1–O1A	112.3(2)

Table 7 Selected torsion angles (°) for ligands **1A** and **1B**, and cocrystalizing molecule **1C** in crystal **5**

	1A	**1B**	**1C**
O1–C2–C3–C10	179.8(8)	−178.6(8)	174.9(8)
C11–C2–C3–C10	4.1(15)	0.9(16)	2.4(15)
C12–O4–C6–C7	177.0(10)	−179.7(8)	−174.8(7)
C12–O4–C6–C5	5.2(16)	1.3(13)	5.1(12)
C5–C6–C7–C8	174.8(8)	−175.1(8)	177.2(8)
C8–C7–C7A–O1	1.3(12)	−4.7(12)	2.2(13)
C8–C7–C7A–C3A	−178.5(8)	173.9(7)	−177.7(7)
C7A–C7–C8–O5	11.3(13)	34.8(12)	156.9(10)
C6–C7–C8–O5	−169.7(9)	−148.4(8)	−20.3(15)
C7A–C7–C8–C9	−165.9(9)	−144.1(9)	−21.4(13)
C6–C7–C8–C9	13.1(15)	32.7(14)	161.4(8)
C3–C2–C11–O2	−5.3(14)	171.6(9)	−8.7(14)
O1–C2–C11–O2	179.2(7)	−8.8(12)	179.2(8)
C3–C2–C11–O3	176.4(8)	−3.7(15)	173.5(8)
O1–C2–C11–O3	0.9(11)	175.9(7)	1.3(10)

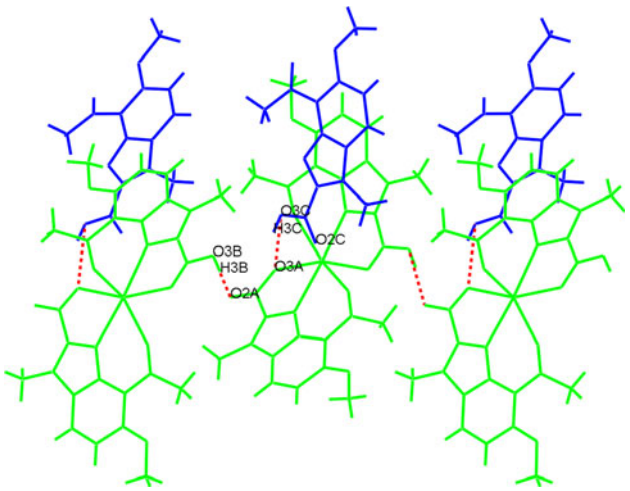


Fig. 10 Hydrogen-bonding pattern in crystal **5**. Donor (D)···acceptor (A) distances are O3B···O4A 2.476(7) Å and O3C···O3A 2.675(7) Å. The D–H···A angles are O3B–H3B···O4A 160° and O3C–H3C···O3A 145°

The comparison of stereochemistry of the acid molecules observed in the complex **5** with results of the theoretical analysis indicates that the molecule **1B** corresponds to the conformer **1.2** from quantum-chemical calculations, while **1C** has the same geometry as the conformer **1.3** (Figs. 6, 8).

Crystal structure

Two intermolecular O–H···O hydrogen bonds, present in the crystal structure of **5**, link together the carboxyl and carboxylate groups in the following pattern: $(COOH)_B\cdots(COO^-)_A\cdots(COOH)_C$, in which the anion **1A** acts as a double acceptor. It joins the acid molecules **1B** and **1C** through the **O**3C–**H**3C···**O**3A and **O**3B–**H**3B···**O**4A ($x + 1/2$, $1/2 - y$, $z + 1/2$) hydrogen bonds. Thus, the monomeric neutral complexes form folded chains along the [101] direction (Fig. 10). In addition, the crystal structure of **5** is stabilized by the C–H···O contacts. These interactions arrange the complex units into the layers crossing along the *c* axis at an angle of about 70°, shown in Fig. 9.

Conclusion

The central part of the analyzed molecules, the heterocyclic benzo[*b*]furan system, is rigid and the C_{Ar}–C and C_{Ar}–O bonds connecting the aromatic nucleus and substituted small functional groups are coplanar. Thus, the structural changes may occur only by a rotation of these substituents, i.e., the acetyl, carboxyl, hydroxyl, and/or methoxy groups. The series of conformers for the derivatives of 2- and 3-benzo[*b*]furancarboxylic acids in the crystalline and gas phase has been described. In both phases, the *ortho*-position of hydroxyl and acetyl groups forces the presence of the O–H···O intramolecular hydrogen bond, closing the six-membered ring.

The $COOH/COOCH_3$ fragment is always coplanar with the aromatic system. In the gas phase, two substituents of the furan ring—the carboxyl and methyl groups—adopt the *cis* and *trans* orientations, while in the solid phase only one form is present. The C=O and C–CH_3 bonds are *trans* for the derivatives of 2-benzo[*b*]furancarboxylic acid (**1**, **2**), and *cis* for the derivatives of 3-benzo[*b*]furancarboxylic acid (**3**, **4**). The *trans* conformation, energetically less favorable, observed in the crystals of **1** and **2**, is probably induced by intermolecular forces. In the solid phase, the OH group of COOH substituent adopts the synplanar form of **O=**C–O**–H** bonds, whereas for the gas phase, two conformations are observed: antiplanar and energetically more favorable—synplanar.

The structural analysis of the sodium complex of acid **1** confirmed the existence of the ligand conformers identified by the quantum chemistry methods. Within the neutral complex unit, of the stoichiometry $[\mathbf{Na^+}\cdot\mathbf{1A^-}\cdot\mathbf{1B}]\cdot\mathbf{1C}$, the organic moieties (**1A**–**C**) differ in the orientation of both the acetyl and carboxyl groups. The ligands **1A** and **1B** are tridentate chelating to the metal cation, whereas the molecule **1C** cocrystallizes outside of the Na^+ coordination sphere.

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